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S15-US2

PATENT

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3/9/06
Date

Michelle H. Olson
Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

WOLFFE et al.

Serial No.: 10/083,682

Filing Date: October 24, 2001

Title: **LIBRARIES OF REGULATORY
SEQUENCES; METHODS OF MAKING AND
USING SAME** (as amended)

Examiner: S. Zhou

Group Art Unit: 1631

Confirmation No.: 1541

Customer No.: 20855

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

X Reply Brief (15 pages) with attached Claims Appendix (3 pages)

X Return receipt postcard


The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	10	- 124	0	x \$50.00	\$0
Independent Claims	1	- 23	0	x \$200.00	\$0
Multiple dependent claims not previously presented, add \$360.00					\$0
Total Amendment Fee					\$0
Small Entity Reduction (if applicable)					\$0
TOTAL FEE DUE					\$0

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: March 9, 2006

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

A.P. Wolffe *et al.*

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Filed: October 24, 2001

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SEQUENCES, METHODS OF
MAKING AND USING SAME (as
amended)

Examiner: S. Zhou

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REPLY BRIEF

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3/9/06 Michelle Hobson
Date Signature

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Examiner: S. Zhou

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REPLY BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

Pursuant to Section 41.37(c) (69 Fed. Reg. 49962, Aug 2004), Appellants submit the following Reply Brief in Response to the Examiner's Answer mailed on January 12, 2006. A Reply Brief submitted within two months of the date of mailing of the Examiner's Answer, namely by March 12, 2006, is timely filed. Appellants respectfully request that the decision of the Examiner be reversed.

STATUS OF THE CLAIMS

Claims 66-71 and 125-128 are on appeal and remain rejected under 35 U.S.C. § 102(b).

GROUND OF REJECTION

1. Claims 66-71 and 125-128 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by pages 177-183 of the Clontech Catalog (hereinafter "Clontech").

ARGUMENTS

Appellants note with appreciation that the rejections under 35 U.S.C. § 112, 1st paragraph, written description have been withdrawn.¹

1. Claims 66-71 and 125-128 Are Not Anticipated by Clontech

However, the rejection of all pending claims as allegedly anticipated by the Clontech catalog was reiterated in the Examiner's Answer.² As before, the rejection under 35 U.S.C. § 102(b) is premised on the assertion that the claimed product (*i.e.*, a library containing inserts consisting essentially of accessible regions of cellular chromatin, produced by contacting cellular chromatin with a probe and selectively cloning polynucleotide fragments containing one end generated by the probe) is indistinguishable from Clontech's genomic libraries (produced by digesting naked DNA with Sau3AI and MboI and cloning size-selected fragments):

Clontech Catalog discloses multiple genomic libraries made from cellular chromatin of different organisms using different vector systems. [citation omitted]. These genomic libraries are made by a method involving digesting genomic DNA, which is from cellular chromatin, of the different organisms with

¹ Examiner's Answer, page 3

² Examiner's Answer, pages 4-5

restriction enzymes, Sau3AI and MboI, which are four cutters and are known in the art to digest the genomes with high frequency, and cloning the digested fragments in different vector systems.³

The Examiner also continues to assert that the use of the transitional phrase “consisting essentially of” does not distinguish the claimed libraries (in which every member contains sequences corresponding to accessible regions of cellular chromatin) from Clontech’s libraries, in which many members contain only sequences corresponding to non-accessible regions, on the grounds that (1) it is not clear from the claims or specification that a library of accessible regions is the basic and novel feature of the claimed libraries and (2) the scope of the phrase “consisting essentially of” is not defined:

Firstly, while Appellant argues in the brief that the basic and novel characteristics of the claimed invention are isolating sequences of accessible regions of cellular chromatin (page 13), there is no clear indication in the specification or claims that these actually are the basic and novel characteristics of the invention. Further, appellant does not define the scope of the phrase “consisting essentially of” for purposes of its patent by making clear in its specification what it regards as constituting a material change in the basic and novel characteristics of the invention. In other words, no indication of what should be included and excluded from the phrase “consisting essentially of” [is given]. Thus, the term “consisting essentially of” is construed as equivalent to “comprising” and is open to any unlisted components.⁴

For the reasons of record, which are reiterated herein and elaborated below, Appellants assert that the specification, as well as the claims, provide a clear indication of the basic and novel properties of the claimed subject matter; thus making clear how inclusion of any unlisted ingredient would materially affect these basic and novel properties. Furthermore, the evidence of record clearly establishes that Clontech’s libraries are produced by methods that necessarily result in a different product than that claimed.

Therefore, Appellants again submit that the rejection is unsustainable.

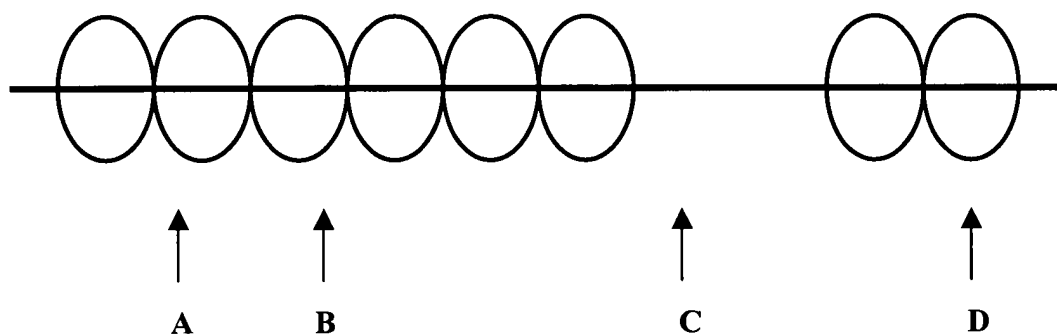
³ Examiner’s Answer, page 4

⁴ Examiner’s Answer, page 7

(a) Comparison Between The Claimed Subject Matter And The Disclosure Of The Reference

Appellants review the particular process steps of the claimed methods, contrasting them with the process steps disclosed by Clontech.

The first step in the construction of the claimed libraries is the treatment of cellular chromatin with a probe of chromatin structure such as, for example, a nuclease.⁵ Cellular chromatin comprises genomic DNA and associated chromosomal proteins, the chromosomal proteins often being assembled into structures called nucleosomes, which serve to condense the genomic DNA.⁶ A schematic representation of cellular chromatin might look as follows:



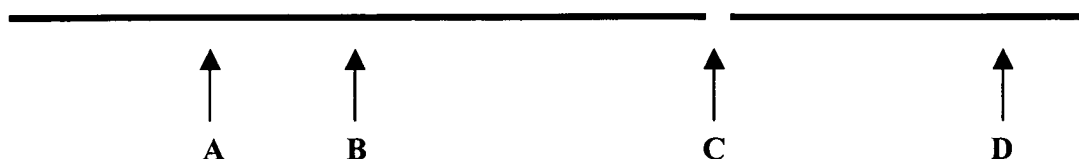
In this diagram, the horizontal line represents genomic DNA and the ovals represent nucleosomes. It can be seen from the diagram that, while the bulk of genomic DNA is covered by nucleosomes, certain regions are devoid of nucleosomes and thereby accessible to probes of chromatin structure. If such a sample of cellular chromatin is contacted with a probe having cleavage sites within the genomic DNA at the positions indicated by the arrows in the diagram above, cleavage will occur only at the site represented by the arrow labeled "C", since cleavage sites A, B and D are inaccessible to the probe, being blocked by the nucleosomes.⁷

⁵ Claim 66 step (a), claim 125

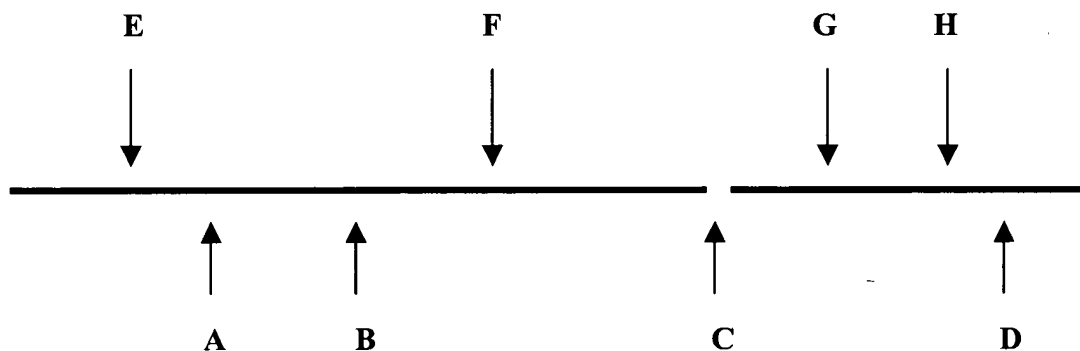
⁶ See, for example, the specification at page 18, lines 13-24

⁷ This corresponds to step (a) of claim 66

Deproteinization of the sample⁸ will yield naked DNA which has been cleaved at the accessible site represented by arrow C, as shown below.



According to the method recited in claim 66, the DNA is then digested with a nuclease (whose cleavage sites are indicated by the arrows labeled E, F, G and H in the diagram below)⁹



Since the substrate for the nuclease digestion step is naked DNA, all of sites E, F, G and H are accessible and will be cleaved, leading to the generation of fragments EF, FC, CG and GH. Importantly, while both ends of fragments EF and GH are generated by nuclease used in step (c), fragments FC and CG comprise one end (at site C) that was generated by cleavage with the probe during step (a). It is these fragments that are selectively cloned in step (d).

⁸ corresponding to step (b) of claim 66

⁹ corresponding to step (c) of claim 66

Thus, by virtue of the process limitations of claim 66, each and every member of the claimed libraries contains sequences from an accessible region of cellular chromatin, providing the basic and novel feature of the claimed libraries.¹⁰

By contrast, the libraries disclosed by Clontech result from digestion of naked DNA with a restriction enzyme, followed by size-selection of the digestion products, and cloning of a particular size fraction.¹¹ Using the same nomenclature from the schematic example provided above, a Clontech library would contain inserts corresponding to fragments AB, BC and CD (in contrast with fragments FC and CG that would be present in the claimed library). It is thus clear that the Clontech libraries contain a class of insert that is not present in the claimed libraries, namely inserts (such as fragment AB) containing entirely non-accessible sequences.¹²

Throughout prosecution, the fact that cellular chromatin is not used as the starting material in the construction of the Clontech libraries, and the consequences of this fact for the structure of the libraries so obtained, has been ignored by the Examiner. A typical statement is found at page 4 of the Examiner's Answer:

Clontech Catalog discloses multiple genomic libraries
made from **cellular chromatin** of different organisms using
different vector systems. (emphasis added)

The Examiner thus incorrectly equates cellular chromatin with naked DNA, despite the fact that both the specification (see above) and the art as a whole teach that they are different substances with different structures and different properties. Furthermore, the fact that

¹⁰ In this example, fragments FC and CG contain sequences from both an accessible and non-accessible regions. If, however, site F were present in the accessible region, then fragment FC would consist entirely of accessible region sequences.

Yet another possibility is that two (or more) sites cleaved by the probe are present in a single accessible region. In this case, fragments having both ends generated by the probe can also be selectively cloned (*see, e.g.* Examples 9 and 10)

¹¹ *See* Clontech catalogue, page entitled "CLONTECH Library Information," section entitled "Library Preparation," second bullet point

¹² Appellants also note in passing that the fact that the Clontech libraries are obtained by partial digestion (see footnote 11 above) undercuts the arguments, based on frequency of digestion by four-cutters, advanced on pages 4 and 5 of the Examiner's Answer.

Appellants use cellular chromatin as the starting material for construction of their libraries, while Clontech uses naked DNA, results in the production of libraries with different basic features, as described above.

Appellants now address, in turn, the specific arguments presented in the Examiner's answer.

(b) The Basic And Novel Properties Of The Claimed Subject Matter Are Defined

Contrary to the allegations in the Examiner's Answer, the claims and specification make abundantly clear the basic and novel properties of the claimed libraries, by defining what the phrase "consisting essentially of" includes and what is excluded.

Indeed, the claims clearly indicate that the novel and basic property of the invention is a library containing insert sequences that "consist essentially of accessible regions of cellular chromatin."¹³ In addition, the preamble and method steps of the claims also make clear that the novel property of the claimed libraries is that they contain inserts consisting essentially of accessible regions.¹⁴ Thus, based on the claims alone, a library containing inserts that correspond only to inaccessible regions (as do the Clontech libraries, see above) is plainly excluded by the use of the transitional phrase "consisting essentially of" in the claims on appeal.

Like the claims, the specification also plainly indicates that the basic property of the claimed invention is the fact that every member of the library contains an insert corresponding to accessible regions of cellular chromatin:

Disclosed herein are methods for identifying and isolating accessible regions of cellular chromatin and/or regulatory regions (*e.g.*, regulatory sequence elements), for example, using one or more various chemical and/or enzymatic probes. Accessibility of such sequences (*e.g.*, regulatory elements) can be a consequence, for example, of a unique local chromatin architecture, reflecting the accessibility of these sequences to transcription factors, or can be indicative of the

¹³ See, Claim 66, lines 3-4 of attached Claims Appendix

¹⁴ See, Claim 66, preamble and step (a) of attached Claims Appendix

presence of one or more transcription factors bound to these sequences. Identification of regulatory sequences by the methods disclosed herein allows their isolation, facilitating the construction of libraries of cell-specific regulatory regions. In addition, determination of the nucleotide sequences of a collection of gene regulatory elements present in a regulatory region library allows construction of databases of cell-specific regulatory regions.¹⁵

The present disclosure provides methods for the identification, isolation and characterization of regulatory DNA sequences in a cell of interest . . . These methods are based in part upon the recognition that regulatory sequences can be identified based upon differences of accessibility for these regions as compared to other regions of cellular chromatin.¹⁶

Therefore, both the claims and specification clearly indicate that the novel and basic property of the claimed libraries is that they contain inserts corresponding to accessible regions and exclude inserts corresponding solely to inaccessible regions. In other words, the phrase “consisting essentially of” can be interpreted (in light of the claims and specification), to encompass libraries having inserts corresponding to accessible regions, including libraries with inserts corresponding only to accessible regions as well as libraries with inserts containing both accessible and inaccessible regions. By the same token, the phrase “consisting essentially of” clearly excludes libraries whose inserts correspond only to inaccessible regions.

Appellants further note that the Examiner’s assertion that the use of the term “comprising” in step (d) of independent claim 66 indicates that what is produced is a clone including both accessible and inaccessible regions is untenable.¹⁷

As a threshold matter, Appellants note (for the reasons detailed above) that clones including both accessible and inaccessible regions are encompassed by the clear definition of the phrase “consisting essentially of.” Only library members having inserts that do not include sequences corresponding to accessible regions are excluded from the scope of the claims. Thus,

¹⁵ See, page 3, line 31 to page 4, line 7 of the specification

¹⁶ See page 26, line 32 through page 27, line 6 of the specification

¹⁷ Examiner’s Answer, paragraph bridging pages 8-9

it is irrelevant whether the selective cloning of step (d) produces a clone including both accessible and inaccessible regions. As long as the clone includes sequences corresponding to accessible regions, it is encompassed by the claims.

Appellants further note that it is impossible for the selective cloning step of step (d) to change the nature of the claimed libraries so as to encompass inserts corresponding only to inaccessible regions. Step (d) refers specifically to cloning of DNA fragments. At most, any DNA fragment can comprise two ends. Accordingly, as used in step (d) of claim 66, the phrase “comprising” refers to a fragment that has at least one end (and at most two ends) generated by probe cleavage as set forth in step (a). Since only accessible regions are susceptible to probe cleavage (as set forth in step (a) of claim 66), only fragments corresponding to accessible regions will comprise one end generated by probe cleavage.

Therefore, in point of fact, the cloning step of step (d), including the use of the term “comprising” as it applies to selective cloning, is yet another indication that the claimed library inserts consist essentially of accessible regions; and actually supports the position that the claims clearly define the basic and novel properties of the invention.

In any event, it is unambiguous (and instantly recognizable) that the basic and novel property of the claimed invention is a library in which the inserts include sequences corresponding to accessible regions. In addition, it is clear that the claims exclude a library in which the inserts correspond only to inaccessible regions.

(c) The Presence of Inaccessible Regions Would Materially Change the Basic and Novel Properties of the Claimed Polynucleotides

Appellants have also met their burden of showing that a library containing inserts corresponding only to non-accessible regions would materially change the characteristics of the claimed polynucleotides.

As noted above, the specification clearly sets forth that basic and novel property of the claimed polynucleotides is that they include sequences corresponding to accessible regions.

Moreover, the specification plainly indicates how accessible regions are materially different from inaccessible regions, for example by virtue of their accessibility to transcriptional regulatory proteins.¹⁸ Hence, there is a defined and well-understood material difference between accessible and inaccessible regions, for example in terms of function – the former includes regulatory regions that can be immediately bound by transcriptional regulators while the latter does not.

Certainly, the fact that accessible regions and inaccessible regions differ significantly in terms of their disclosed ability to act as regulatory regions establishes that including inserts that correspond solely to inaccessible regions (and do not include accessible regions) would materially change the basic property of the claimed subject matter.¹⁹

(d) Clontech Does Not Disclose Each And Every Element Of the Pending Claims

As outlined above, it is an error to assert that Clontech discloses the recited method steps of the pending claims or, moreover, that Clontech discloses the claimed product as obtained by the particular method steps.

As previously pointed out by Appellants, the Clontech catalogue discloses nothing more than genomic libraries obtained by digestion of naked DNA.²⁰ No evidence has been presented that Clontech digests cellular chromatin, as set forth in the method steps of the claims.²¹ Thus, the totality of the record shows that Clontech does not describe or demonstrate the claimed methods steps of contacting cellular chromatin with a probe that cleaves the cellular chromatin at accessible regions of cellular chromatin; and/or deproteinizing the cleaved cellular chromatin -- essential elements of each and every pending claim. Rather, Clontech describes a library (and

¹⁸ See, page 3, line 31 to page 4, line 3 of the specification, reproduced above

¹⁹ For example, a coding sequence could be inserted downstream of an accessible region sequence, to obtain regulation of expression of the coding sequence by the accessible region sequence. No such regulation of a coding sequence would be obtained by placing it downstream of a non-accessible region sequence.

²⁰ See, *e.g.*, Appeal Brief, pages 13-14; Responses dated December 8, 2004 and May 24, 2005

²¹ See, *e.g.*, Appeal Brief, pages 13-14; Office Action dated September 9, 2004 at page 12; Office Action dated March 31, 2005 at page 8 and Advisory Action dated June 21, 2005 at page 2

library members) made from naked DNA, a substance that is very different from cellular chromatin (see above).

Moreover, because Clontech produces their libraries by digesting naked DNA (rather than cellular chromatin), it is inevitable that Clontech's libraries are distinct from the claimed product in that Clontech's libraries will necessarily include inserts corresponding only to non-accessible regions – embodiments excluded by the language of the claims on appeal.

As noted in Section 2133 of the M.P.E.P., when the claimed product of a product-by-process claim is defined structurally by the process steps, these steps must be considered when assessing patentability of the product so-produced:

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. *See, e.g., In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (holding "interbonded by interfusion" to limit structure of the claimed composite and noting that terms such as "welded," "intermixed," "ground in place," "press fitted," and "etched" are capable of construction as structural limitations.)

Therefore, in the case on appeal, the structure of the claimed product implied by digestion of cellular chromatin as claimed must be considered when assessing the patentability of the resulting libraries. It is clear that digestion of naked DNA **cannot**, under any circumstances, produce a library of polynucleotides consisting essentially of accessible regions (and excluding polynucleotides corresponding only to inaccessible regions), as claimed. This is because cellular chromatin, by definition, includes proteins that protect inaccessible regions from digestion with a probe. There are **no** proteins complexed with the naked DNA used to make Clontech's libraries and, accordingly, there is no distinction between accessible and inaccessible regions in Clontech's method; nor does Clontech teach how to clone only fragments comprising an accessible region, as claimed. Clontech's libraries necessarily include inserts that include **only** inaccessible sequences, which are not only distinguishable from the claimed product, but, in addition, clearly excluded by the claims on appeal.

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Thus, the claimed product is unambiguously distinguishable from Clontech's product and, accordingly, Clontech cannot anticipate the pending claims.

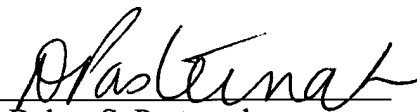
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CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are patentable over the art cited by the Examiner. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: March 9, 2006

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CLAIMS APPENDIX

CLAIMS ON APPEAL

1 to 65. (canceled).

66. (previously presented) A polynucleotide, wherein the polynucleotide is a member of a library of polynucleotides, the members of the library comprising a vector and an insert, wherein the insert sequences consist essentially of accessible regions of cellular chromatin, wherein the library is obtained according to the method of:

(a) contacting cellular chromatin with a probe, wherein reaction of the probe with cellular chromatin results in polynucleotide cleavage at accessible regions of cellular chromatin;

(b) deproteinizing the cleaved chromatin of step (a);

(c) digesting the deproteinized chromatin of step (b) with a nuclease to generate a collection of polynucleotide fragments; and

(d) selectively cloning polynucleotide fragments comprising one end generated by probe cleavage.

67. (previously presented) A library comprising a plurality of polynucleotides according to claim 66.

68. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from cells at a particular stage of development.

69. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from cells of a particular tissue.

70. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from diseased cells.

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71. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from infected cells.

72 to 124. (canceled).

125. (previously presented): The polynucleotide of claim 66, wherein, in step (a), the probe is a nuclease.

126. (previously presented): The polynucleotide of claim 125, wherein the nuclease is a restriction enzyme.

127. (previously presented): The polynucleotide of claim 126, wherein the probe comprises a plurality of restriction enzymes.

128. (previously presented): The polynucleotide of claim 66, wherein, in step (c), the nuclease is a restriction enzyme.